DRUG DEVELOPMENT

R&D for long COVID is collapsing

Public and private funding is lacking, scrambling opportunities to develop treatments

by ***Rowan Walrath***

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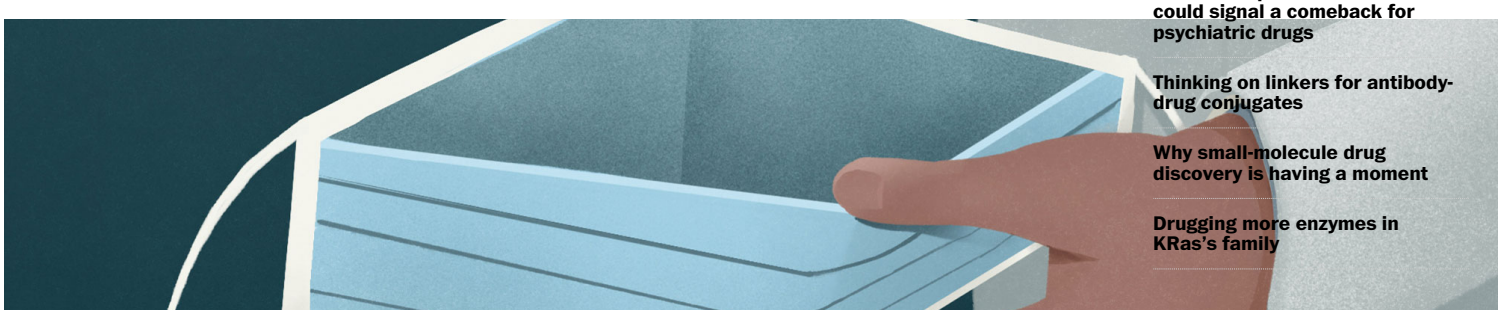

Credit: Elia Sampò | Funding for new long COVID treatments is severely lacking, scrambling research and development.

When COVID-19 hit, the biotechnology company Aim ImmunoTech was developing a drug for myalgic encephalomyelitis/chronic fatigue syndrome, better known as ME/CFS. As more people came down with COVID-19, some began to describe lingering problems that sounded a lot like ME/CFS. In many cases, people who got sick simply never seemed to get better. In others, they recovered completely—or thought they had—only to be waylaid by new problems: fatigue that wouldn't go away with any amount of rest, brain fog that got in the way of normal conversations, a sudden tendency toward dizziness and fainting, or all the above.

There was a clear overlap between the condition, which patients began calling long COVID, and ME/CFS. People with ME/CFS have a deep, debilitating fatigue. They cannot tolerate much, if any, exercise; walking up a slight incline can mean days of recovery. Those with the most severe cases are bedbound.

Aim's leaders set out to test whether the company's drug, Ampligen, which is approved for ME/CFS in Argentina but not yet in the US, might be a good fit for treating long COVID. They started with a tiny study, just 4 people. When most of those participants responded well, they scaled up to 80. While **initial data were mixed**, people taking Ampligen were **generally able to walk farther** in a 6 min walk test than those who took a placebo, indicating improvement in baseline fatigue. The company is now making plans for a follow-on study in long COVID.

Aim's motivation for testing Ampligen in long COVID was twofold. Executives believed they could help people with the condition, given the significant overlap in symptoms with ME/CFS. But they also, plainly, thought there'd be money. They were wrong.

"When we first went out to do this study in long COVID, there was money from . . . RECOVER," Aim scientific officer Chris McAleer says, referring to Researching COVID to Enhance Recovery

IN BRIEF

Long COVID is a difficult therapeutic area to work in. It's a scientifically challenging condition, but perhaps more critically, few want to fund new treatments. Private investors, Big Pharma, and government agencies alike see long COVID as too risky as long as its underlying mechanisms are so poorly understood. This dynamic has hampered the few biotechnology and pharmaceutical companies trying to develop new medicines. The lack of funding has frustrated people with long COVID, who have few options available to them. And crucially, it has snarled research and development, cutting drug development short.

(RECOVER), the National Institutes of Health's $1.7 billion initiative to fund projects investigating causes of, and potential treatments for, long COVID. McAleer says Aim attempted to get RECOVER funds, "believing that we had a therapeutic for these individuals, and we get nothing."

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Instead of funding novel medicines like Ampligen, the NIH has directed most of its RECOVER resources to observational studies designed to learn more about the condition, not treat it. Only last year did the agency begin to fund clinical trials for long COVID treatments, and those investigate the repurposing of approved drugs. What RECOVER is not doing is funding new compounds.

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RECOVER is the only federal funding mechanism aimed at long COVID research. Other initiatives, like the $3 billion Project NextGen and the $577 million Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern, put grant money toward next-generation vaccines, monoclonal antibodies, and antivirals for COVID-19. They stop short of testing those compounds as long COVID treatments.

Private funding is even harder to come by. Large pharmaceutical companies have mostly stayed away from the condition. (Some RECOVER trials are testing **Pfizer's COVID-19 antiviral Paxlovid**, but a Pfizer spokesperson confirms that Pfizer is not sponsoring those studies.) Most investors have also avoided long COVID: a senior analyst on PitchBook's biotech team, which tracks industry financing closely, says he isn't aware of any investment in the space.

"What you need is innovation on this front that's not driven by profit motive, but impact on global human health," says Sumit Chanda, an immunologist and microbiologist at Scripps Research who coleads one of the AViDD centers. "We could have been filling in the gaps for things like long COVID, where pharma doesn't see that there's a billion-dollar market."

> **"It is seen by the industry and by investors as a shot in the dark."**
>
> — ***Radu Pislariu,*** *cofounder and CEO of Laurent Pharmaceuticals*

The few biotech companies that are developing potential treatments for long COVID, including Aim, are usually funding those efforts out of their own balance sheets. Experts warn that such a pattern is not sustainable. At least four companies that were developing long COVID treatments have shut down because of an apparent lack of finances. Others are evaluating a shift away from long COVID.

"It is seen by the industry and by investors as a shot in the dark," says Radu Pislariu, cofounder and CEO of Laurent Pharmaceuticals, a start-up that's developing an antiviral and anti-inflammatory for long COVID. "What I know is that nobody wants to hear about COVID. When you say the name COVID, it's bad . . ., but long COVID is not going anywhere, because COVID-19 is endemic. It will stay. At some point, everyone will realize that we have to do more for it."

'TIME AND PATIENCE AND MONEY'

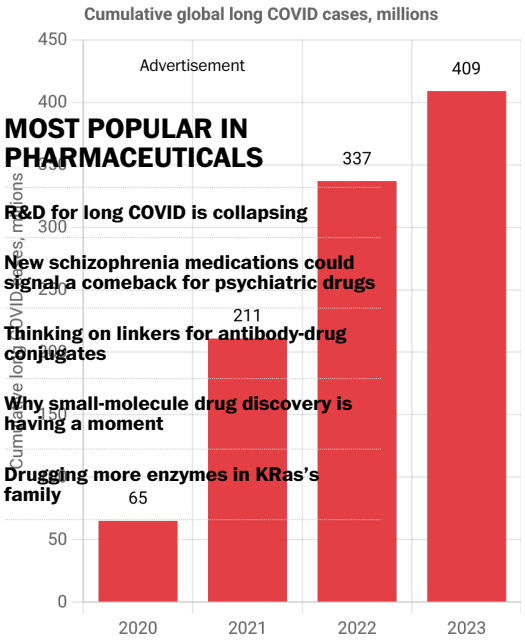
Much of the hesitancy to make new medicines stems from the evasive nature of long COVID itself. The condition is multisystemic, affecting the brain, heart, endocrine network, immune system, reproductive organs, and gastrointestinal tract. While researchers are finding increasing evidence for some of the disease's mechanisms, like viral persistence, immune dysregulation, and mitochondrial dysfunction, they might not uncover a one-size-fits-all treatment.

"Until we have a better understanding of the underlying mechanisms of long COVID, I think physicians are doing the best they can with the information they have and the guidance that is available to them," says Ian Simon, director of the US Department of Health and Human Services' Office of Long COVID Research and Practice. The research taking place now will eventually guide new therapeutic development, he says.

Meanwhile, time marches on.

COVID-19'S LONG TAIL

The cumulative global incidence of long COVID has more than sextupled since 2020.



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Source: *Nat. Med.* 2024, DOI: 10.1038/s41591-024-03173-6.

By the end of 2023, more than 409 million people worldwide had long COVID, according to a recent review coauthored by two cofounders of the Patient-Led Research Collaborative (PLRC) and several prominent long COVID researchers (*Nat. Med.* 2024; DOI: **10.1038/s41591-024-03173-6**). Most of those 409 million contracted COVID-19 and then long COVID after vaccines and antivirals became available. That fact undercuts the notion that the condition results only from severe cases of COVID-19 contracted before those interventions existed. (Vaccination and treatment with antivirals do correlate with a lower incidence of long COVID but don't prevent it outright.)

"There is that narrative that long COVID is over," says Hannah Davis, cofounder of the PLRC and a coauthor of the review, who has had long COVID since 2020. "I think that's fairly obviously not true."

The few biotech companies that have taken matters into their own hands, like Aim, are often reduced to small study sizes with limited time frames because they can't get outside funding.

InflammX Therapeutics, a Florida-based ophthalmology firm headed by former Bausch & Lomb executive Brian Levy, started testing an anti-inflammatory drug candidate called Xiflam after Levy's daughter came down with long COVID. Xiflam is designed to close connexin 43 (Cx43) hemichannels when they become pathological. The hemichannels, which form in cell membranes, would otherwise allow intracellular adenosine triphosphate (ATP) to escape and signal the NLRP3 inflammasome to crank up its activity, causing pain and inflammation.

InflammX originally conceived of Xiflam as a treatment for inflammation in various eye disorders, but after Levy familiarized himself with the literature on long COVID, he figured the compound might be useful for people like his daughter.

InflammX set up a **small Phase 2a study** at a site just outside Boston. The trial will enroll just 20 participants, including Levy's daughter and InflammX's chief operating and financial officer, David Pool, who also has long COVID. The study is set up such that participants don't know if they're taking Xiflam or a placebo.

Levy says the company tried to communicate with NIH RECOVER staff multiple times but never heard back. "We couldn't wait," he says.

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— ***Hannah Davis,*** *cofounder of the Patient-Led Research Collaborative*

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Larger firms are similarly disconnected from US federal efforts. COVID-19 vaccine maker Moderna appointed a vice president of long COVID last year. Bishoy Rizkalla now oversees a small team studying how the company's messenger RNA shots could mitigate problems caused by new and latent viruses, including SARS-CoV-2. But Rizkalla says Moderna has no federally funded projects in long COVID.

Federal bureaucracy has slowed down research in other ways. When long COVID appeared, Tonix Pharmaceuticals was developing a possible drug called TNX-102 SL to treat fibromyalgia. The two conditions look similar: they're painful, fatiguing, and multisystemic, and fibromyalgia can crop up after a viral infection.

But it wasn't easy to design a study to test the compound in long COVID. Among other issues, the US Food and Drug Administration initially insisted that participants have a positive COVID-19 test confirmed by a laboratory, like a polymerase chain reaction test, to be included in the study. At-home diagnostics wouldn't count.

"We spent a huge amount of money, and we couldn't enroll people who had lab-confirmed COVID because no one was going to labs to confirm their COVID," cofounder and CEO Seth Lederman says. "We just ran out of time and patience and money, frankly."

Tonix had planned to enroll 450 participants. The company ultimately enrolled only 63. **The study failed to meet its primary end point** of reducing pain intensity, a result Lederman attributes to the smaller-than-expected sample size.

TNX-102 SL trended toward improvements in fatigue and other areas, like sleep quality and cognitive function, but Tonix is moving away from developing the compound as a long COVID treatment and focusing on developing it for fibromyalgia. If it's approved, Lederman hopes that physicians will prescribe it to people who meet the clinical criteria for fibromyalgia regardless of whether their condition stems from COVID-19.

"I'm not saying we're not going to do another study in long COVID, but for the short term, it's deemphasized," Lederman says.

ABANDONED ATTEMPTS

Without more public or private investment, it's unclear how research can proceed. The small corner of the private sector that has endeavored to take on long COVID is slowly becoming a graveyard.

Axcella Therapeutics made a big gamble in late 2022. The company pivoted from trying to treat nonalcoholic steatohepatitis, a liver disease, to addressing chronic fatigue in people with long COVID. In doing so, Axcella reoriented itself exclusively around long COVID, laying off most of its staff and abandoning other research activities. People in a 41-person Phase 2a trial of the drug candidate, AXA1125, showed improvement in fatigue scores based on a clinical questionnaire (*eClinicalMedicine* 2023, DOI: **10.1016/j.eclinm.2023.101946**), but Axcella shut down before it could get its planned 300-person follow-on study up and running.

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The fate of AXA1125 may be to gather dust. Axcella's former executives have moved on to other pursuits. Erstwhile chief medical officer Margaret Koziel, once a champion of AXA1125, says by

email that she is “not up to date on current research on long COVID.” Staff at the University of Oxford, which ran the Phase 2a study, were not able to procure information about the planned Phase 2b/3 trial. A spokesperson for Flagship Pioneering, the venture firm that founded Axcella in 2011, declined to comment to C&EN.

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Other firms have met similar ends. **Ampio Pharmaceuticals dissolved** in August after completing only a Phase 1 study to evaluate an inhaled medication called Ampion in people with long COVID who have breathing issues. Biotech firm SolAeroMed shut down before even starting a trial of its inhaled drug for people with long COVID. “Unfortunately we were unable to attract funding to support our clinical work for COVID,” CEO John Dennis says by email.

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Another biotech company, Aerium Therapeutics, did manage to get just enough of its monoclonal antibody AER002 manufactured and in the hands of researchers at the University of California, San Francisco, before it **ended operations**. The researchers are now testing AER002 in a Phase 2 trial with people with long COVID. Michael Peluso, an infectious disease clinician and researcher at UCSF and principal investigator of the trial, says that while AER002 may not advance without a company behind it, the study could be valuable for validating long COVID’s mechanisms of disease and providing a proof of concept for monoclonal antibody treatment more generally.

“[Aerium] put a lot of effort into making sure that the study would not be impacted,” Peluso says. “Regardless of the results of this study, doing a follow-up study now that we’ve kind of learned the mechanics of it with modern monoclonals would be really, really interesting.”

‘A SQUANDERED OPPORTUNITY’

In 2022, the NIH’s National Institute of Allergy and Infectious Diseases (NIAID) put about $577 million toward nine research centers that would discover and develop antivirals for various pathogens. Called the Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern, the centers were initially imagined as 5-year projects, enough time to ready multiple candidates for preclinical development. The NIH allocated money for the first 3 years and promised more funds to come later.

The prospect excited John Chodera, a computational chemist at the Memorial Sloan Kettering Cancer Center and a principal investigator at an AViDD center called the AI-Driven Structure-Enabled Antiviral Platform. Chodera figured that if his team were able to develop a potent antiviral for SARS-CoV-2, it could potentially be used to treat long COVID as well. A predominant theory is that reservoirs of hidden virus in the body cause ongoing symptoms.

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But Chodera says NIAID told him and other AViDD investigators that establishing long COVID models was out of scope. And last year, **Congress clawed back unspent COVID-19 pandemic relief funds**, including the pool of money intended for the AViDD centers’ last 2 years. Lawmakers were supposed to come through with additional funding, Chodera says, but it never materialized. All nine AViDD centers will run out of money come May 2025.

“When we do start to understand what the molecular targets for long COVID are going to be, it’d be very easy to pivot and train our fire on those targets,” says Chanda from Scripps’s AViDD center. “The problem is that it took us probably 2 years to get everything up and going. If you cut the funding after 3 years, we basically have to dismantle it. We don’t have an opportunity to say, ‘Hey, look, this is what we’ve done. We can now take this and train our fire on X, Y, and Z.’ ”

Researchers at multiple AViDD centers confirm that the NIH has offered a 1-year, no-cost extension, but it doesn’t come with additional funds. They now find themselves in the same position as many academic labs: seeking grant money to keep their projects going.

Worse, they say, is that applying for other grants will likely mean splitting up research teams, thus undoing the network effect that these centers were supposed to provide.

“Now what we’ve got is a bunch of half bridges with nowhere to fund the continuation of that work,” says Nathaniel Moorman, cofounder and scientific adviser of the Rapidly Emerging Antiviral Drug Development Initiative, which houses an AViDD center at the University of North Carolina at Chapel Hill.

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“This was a squandered opportunity, not just for pandemic preparedness but to tackle these unmet needs that are being neglected by biotech and pharma,” Chanda says.

Ann Kwong has been here before. The virologist was among the first industry scientists trying to develop antivirals for hepatitis C virus (HCV) back in the 1990s. Kwong led an antiviral discovery team at the Schering-Plough Research Institute for 6 years. In 1997, Vertex Pharmaceuticals recruited her to lead its new virology group.

Kwong and her team at Vertex developed a number of antivirals for HCV, HIV, and influenza viruses; one was the HCV protease inhibitor telaprevir. She recalls that a major challenge for the HCV antivirals was that scientists didn’t know where in the body the virus was hiding. Kwong says she had to fight to develop an antiviral that targeted the liver since it hadn’t yet been confirmed that HCV primarily resides there. People with chronic hepatitis C would in many cases eventually develop liver failure or cancer, but they presented with other issues too, like brain fog, fatigue, and inflammation.

She sees the same dynamic playing out in long COVID.

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“This reminds me of HIV days and HCV days,” Kwong says. “This idea that pharma doesn’t want to work on this because we don’t know things about SARS-CoV-2 and long COVID is bullshit.”

Since January, Kwong has been cooking up something new. She’s approaching long COVID the way she did chronic hepatitis C: treating it as a chronic infection, through a start-up called Persistence Bio. Persistence is still in stealth; its name reflects its mission to create antivirals that can reach hidden reservoirs of persistent SARS-CoV-2, which many researchers believe to be a cause of long COVID.

“Long COVID is really interesting because there’s so many different symptoms,” Kwong says. “As a virologist, I am not surprised, because it’s an amazing virus. It infects every tissue in your body. . . . All the autopsy studies show that it’s in your brain. It’s in your gut. It’s in your lungs. It’s in your heart. To me, all the different symptoms are indicative of where the virus has gone when it infected you.”

Kwong has experienced some of these symptoms firsthand. She contracted COVID-19 while flying home to Massachusetts from Germany in 2020. For about a year afterward, she’d get caught off guard by sudden bouts of fatigue, bending over to catch her breath as she walked around the horse farm where she lives, her legs aching. Those symptoms went away with time and luck, but another round of symptoms roared to life this spring, including what Kwong describes as “partial blackouts.”

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>
> — ***Ann Kwong,*** *chief scientific officer of Persistence Bio*

Kwong hasn’t been formally diagnosed with long COVID, but she says she “strongly suspects” she has it. Others among Persistence’s team of about 25 also have the condition.

“Long COVID patients have been involved with the founding of our company, and we work closely with them and know how awful the condition can be,” Kwong says. “It is a big motivator for our team.”

Persistence is in the process of fundraising. Kwong says she's in conversations with private investors, but she and her cofounders are hoping to get public funding too.

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On Sept. 23, the NIH is convening a 3-day workshop to review what RECOVER has accomplished and plan the next phase of the initiative. Crucially, that phase will include additional clinical trials. RECOVER's $1.7 billion in funding includes a recent award of $515 million over the next 4 years. It's not out of the question that this time, industry players might be invited to the table. Tonix Pharmaceuticals' Lederman and Aim ImmunoTech's McAleer will both speak during the workshop.

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The US Senate Committee on Appropriations explicitly directed the NIH during an Aug. 1 meeting to prioritize research to understand, diagnose, and treat long COVID. It also recommended that Congress put $1.5 billion toward the Advanced Research Projects Agency for Health (ARPA-H), which often partners with industry players. The committee instructed ARPA-H to invest in "high-risk, high-reward research . . . focused on drug trials, development of biomarkers, and research that includes long COVID associated conditions." Also last month, Sen. Bernie Sanders (I-VT) introduced the Long COVID Research Moonshot Act, which would give the NIH $1 billion a year for a decade to treat and monitor patients.

It's these kinds of mechanisms that might make a difference for long COVID drug development.

"What I've seen a lot is pharma being hesitant to get involved," says Lisa McCorkell, a cofounder of the PLRC and a coauthor of the recent long COVID review. "Maybe they'll invest if NIH also matches their investment or something like that. Having those public-private partnerships is really, at this stage, what will propel us forward."

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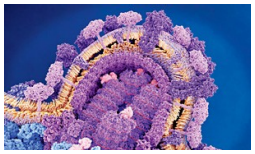

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